fragile XE syndrome

Fragile XE syndrome is a genetic disorder that impairs thinking ability and cognitive functioning. Most affected individuals have mild intellectual disability. In some people with this condition, cognitive function is described as borderline, which means that it is below average but not low enough to be classified as an intellectual disability. Females are rarely diagnosed with fragile XE syndrome, likely because the signs and symptoms are so mild that the individuals function normally.

Learning disabilities are the most common sign of impaired cognitive function in people with fragile XE syndrome. The learning disabilities are likely a result of communication and behavioral problems, including delayed speech, poor writing skills, hyperactivity, and a short attention span. Some affected individuals display autistic behaviors, such as hand flapping, repetitive behaviors, and intense interest in a particular subject. Unlike some other forms of intellectual disability, cognitive functioning remains steady and does not decline with age in fragile XE syndrome.

Frequency

Fragile XE syndrome is estimated to affect 1 in 25,000 to 100,000 newborn males. Only a small number of affected females have been described in the medical literature. Because mildly affected individuals may never be diagnosed, it is thought that the condition may be more common than reported.

Genetic Changes

Fragile XE syndrome is caused by mutations in the *AFF2* gene. This gene provides instructions for making a protein whose function is not well understood. Some studies show that the AFF2 protein can attach (bind) to DNA and help control the activity of other genes. Other studies suggest that the AFF2 protein is involved in the process by which the blueprint for making proteins is cut and rearranged to produce different versions of the protein (alternative splicing). Researchers are working to determine which genes and proteins are affected by AFF2.

Nearly all cases of fragile XE syndrome occur when a region of the *AFF2* gene, known as the CCG trinucleotide repeat, is abnormally expanded. Normally, this segment of three DNA building blocks (nucleotides) is repeated approximately 4 to 40 times. However, in people with fragile XE syndrome, the CCG segment is repeated more than 200 times, which makes this region of the gene unstable. (When expanded, this region is known as the FRAXE fragile site.) As a result, the *AFF2* gene is turned off (silenced), and no AFF2 protein is produced. It is unclear how a shortage of this protein leads to intellectual disability in people with fragile XE syndrome.

People with 50 to 200 CCG repeats are said to have an *AFF2* gene premutation. Current research suggests that people with a premutation do not have associated cognitive problems.

Inheritance Pattern

Fragile XE syndrome is inherited in an X-linked dominant pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, which is one of the two sex chromosomes. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females.

In parents with the *AFF2* gene premutation, the number of CCG repeats can expand to more than 200 in cells that develop into eggs or sperm. This means that parents with the premutation have an increased risk of having a child with fragile XE syndrome. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons; sons receive a Y chromosome from their father, which does not include the *AFF2* gene.

Other Names for This Condition

- FRAXE intellectual deficit
- FRAXE intellectual disability
- FRAXE mental retardation syndrome
- FRAXE syndrome
- mental retardation, X-linked, associated with fragile site FRAXE
- mental retardation, X-linked, FRAXE type

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: FRAXE
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0751157/

Other Diagnosis and Management Resources

- Centers for Disease Control and Prevention: Developmental Screening Fact Sheet
  https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/DevelopmentalScreening.pdf

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Intellectual Disability
  https://medlineplus.gov/ency/article/001523.htm
- Health Topic: Developmental Disabilities
  https://medlineplus.gov/developmentaldisabilities.html

Genetic and Rare Diseases Information Center

- Fragile XE syndrome
  https://rarediseases.info.nih.gov/diseases/2378/fragile-xe-syndrome

Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development: Intellectual and Developmental Disabilities
  https://www.nichd.nih.gov/health/topics/idds/conditioninfo/Pages/default.aspx

Educational Resources

- Centers for Disease Control and Prevention: Intellectual Disability
  https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/IntellectualDisability.pdf
- Disease InfoSearch: Fragile XE Syndrome
  http://www.diseaseinfosearch.org/Fragile+XE+Syndrome/2911
- MalaCards: mental retardation, x-linked, fraxe type
  http://www.malacards.org/card/mental_retardation_x_linked_fraxe_type

- My 46 Trait Profile
  https://www.my46.org/trait-document?trait=Fragile%20XE%20syndrome&parent=Genetic%20Syndromes&type=profile
- Orphanet: FRAXE intellectual disability
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=100973

Patient Support and Advocacy Resources

- Resource List from the University of Kansas Medical Center: Developmental Delay
  http://www.kumc.edu/gec/support/devdelay.html
- The Arc: For People With Intellectual and Developmental Disabilities
  http://www.thearc.org/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28fraxe+intellectual+disability%5BTIAB%5D%29+OR+%28fraxe+syndrome%5BTIAB%5D%29+OR+%28FRAXE%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- MENTAL RETARDATION, X-LINKED, ASSOCIATED WITH FRAGILE SITE FRAXE
  http://omim.org/entry/309548

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